(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 August 2001 (02.08.2001)

PCT

(10) International Publication Number
WO 01/54584 A1

(51) International Patent Classification[7]: A61B 8/08, 5/03

(21) International Application Number: PCT/US00/02196

(22) International Filing Date: 27 January 2000 (27.01.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/117,378 27 January 1999 (27.01.1999) US
09/493,044 27 January 2000 (27.01.2000) US

(71) Applicant: THE GOVERNMENT OF THE UNITED STATES as represented by THE ADMINISTRATOR OF THE NATIONAL AERONAUTICS AND SPACE ADMINISTRATION [US/US]; Nasa Langley Research Center, 3 Langley Boulevard, Mail Stop 212, Hampton, VA 23681-2199 (US).

(72) Inventors: YOST, William; 797 Fawn Lane, Newport News, VA 23602 (US). CANTRELL, John; 245 Queens Drive, Williamsburg, VA 23185 (US).

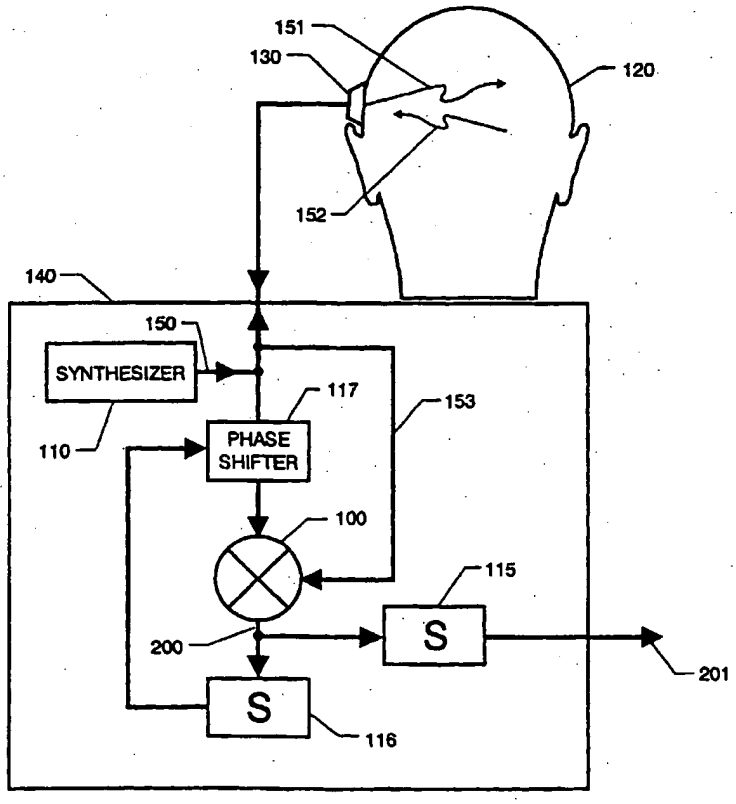
(74) Agents: GALUS, Helen et al.; NASA Langley Research Center, Mail Stop 212, 3 Langley Boulevard, Hampton, VA 23681-2199 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,

[Continued on next page]

(54) Title: ULTRASONIC APPARATUS AND TECHNIQUE TO MEASURE CHANGES IN INTRACRANIAL PRESSURE



(57) Abstract: Changes in intracranial pressure can be measured dynamically and non-invasively by monitoring one or more cerebrospinal fluid pulsatile components. Pulsatile components such as systolic and diastolic blood pressures are partially transferred to the cerebrospinal fluid by way of blood vessels contained in the surrounding brain tissue and membrane. As intracranial pressure varies, these cerebrospinal fluid pulsatile components also vary. Thus, intracranial pressure can be dynamically measured. Furthermore, use of acoustics allows the measurement to be completely non-invasive. In the preferred embodiment, phase comparison of a reflected acoustic signal (152) to a reference signal (151) using a constant frequency pulsed phase-locked-loop ultrasonic device (140) allows the pulsatile components to be monitored. Calibrating the device by inducing a known change in intracranial pressure allows conversion.

WO 01/54584 A1

MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ULTRASONIC APPARATUS AND TECHNIQUE TO MEASURE CHANGES IN INTRACRANIAL PRESSURE

Claim of Benefit of Provisional Application

Pursuant to 35 U.S.C. §119, the benefit of priority from provisional application 60/117,378, with a filing date of January 27, 1999, is claimed for this non-provisional application.

Origin of the Invention

The invention described herein was made in the performance of work done by employees of the United States Government and may be manufactured and used by or for the government for governmental purposes without the payment of any royalties thereon or therefore.

Technical Field

This invention relates generally to measuring intracranial pressure in patients, and more particularly to measuring intracranial pressure by non-invasively monitoring the pulsatile components of cerebrospinal fluid contained within the head.

Background

Intracranial pressure (ICP) is an important parameter in the management of closed head trauma. For example, head trauma can cause edema which leads to increased ICP as well as decreased brain compliance. High ICP must therefore be treated aggressively in order to prevent secondary neurological damage. Conditions, other than trauma, which can lead to elevated ICP include intracerebral hematoma, central nervous system infections, subarachnoid hemorrhage, space-occupying lesions, increased gravitational forces and whole body acceleration. When ICP is elevated, it can vary widely from moment to moment and dynamic measurement of

ICP is extremely useful. Dynamic measurement of ICP may also provide evidence of hypertension before the onset of clinical signs and symptoms.

Most current methods for measuring ICP are invasive, either utilizing an intraventricular catheter, a subarachnoid screw, an epidural pressure sensor or a sound wave burst into the inner ear. The leading complications of invasive ICP monitoring are insertion-related hemorrhage and hematoma formation, acute overdrainage of cerebrospinal fluid, and infection. An example of the generation of a sound wave causing the bones of the middle ear to react and transfer pressure to the eardrum can be found in U.S. Pat. No. 4,841,986 issued to Marchbanks. In addition to the extreme discomfort to the patient resulting from such a method, the results are not very accurate.

Although other methods claim to non-invasively measure ICP, they either measure some physiological quantity that has no fixed relationship to ICP or the relationship only allows for static ICP measurements accompanied by fairly complex calibration schemes. A method described by U.S. Pat. No. 5,617,873 issued to Yost and Cantrell, describes the non-invasive use of a constant frequency pulsed phase-locked-loop (CFPPLL) ultrasonic device to statically measure ICP. While such an ultrasonic technique is painless and effective in reducing the invasiveness of the ICP measurement, other problems are left unsolved. The CFPPLL receives a reflected toneburst signal from the front of the head and phase compares the reflected signal to a reference signal. The difference in phase between the two signals is attributed to changes in cerebrospinal fluid volume which is due to ICP changes. The phase comparison results in a control voltage which represents the amount of voltage required to bring the two signals into quadrature. A pressure-volume index along with a fairly complex calibration scheme utilizing either a tiltable bed or pressurized cap allows for the conversion from control voltage to cerebrospinal fluid volume, to ICP. The limitation associated with such a method, is that the ICP measurements are relatively static because they depend on changes in the cerebrospinal fluid volume, a

relatively static physiological quantity. Furthermore, the device as described lacked sufficient responsiveness to measure dynamic quantities. The calibration scheme is also sufficiently complex to limit the clinical usefulness of the method.

Statement of Invention

Accordingly, one object of the invention is to non-invasively measure ICP within a patient's head.

A further object of the invention is to measure ICP by using a non-invasive ultrasonic measurement device.

A further object of the invention is to monitor physiological quantities such as pulsatile components which enable accurate, dynamic ICP measurements to be made.

Another object is to use a measurement device with sufficient responsiveness to monitor dynamic quantities.

Still another object is to allow measurement of ICP with a relatively simple calibration scheme.

Additional objects and advantages of the present invention are apparent from the drawings and specification which follow.

Summary of the Invention

The present invention monitors one or more blood pressure pulsatile components present in the brain as a method of measuring ICP. Examples of these pulsatile components are systolic and diastolic blood pressures which are partially transferred to the cerebrospinal fluid (CSF) contained in the head. Overall blood pressure is maintained by the complex interaction of the homeostatic mechanisms of the body and is moderated by the volume of the blood, the lumen of the arteries and arterioles, and the force of the cardiac contractions. These cardiac contractions transfer arterial pulses to the blood vessels in the brain tissue and the membrane surrounding the CSF. The blood vessels in turn partially transfer the arterial pulses to

the adjacent CSF. Continuous monitoring of these pulses allows ICP measuring because as the ICP varies, the pulsatile components of the CSF also vary. Capitalizing on this direct relationship for the purpose of non-invasively measuring ICP is not found in the prior art.

The present invention generates an acoustic signal on one side of the head which is reflected back from the other side of the head. As the reflected acoustic signal travels through the brain, pulsatile variations in the CSF cause associated phase variations in the signal. The preferred embodiment of the present invention utilizes the phase shifting capabilities of the CFPPLL described by U.S. Pat. No. 5,214,955 issued to Yost and Cantrell to monitor this variation in the CSF pulsatile components, which patent is herein incorporated by reference, as if set forth in its entirety. After receiving the phase varied acoustic signal and converting it into a phase varied electrical signal, the CFPPLL phase compares the electrical signal to a reference signal, generates an error signal in relation to the difference in phase between the two signals, integrates the error signal into a control voltage, and shifts the phase of the reference signal based on the control voltage such that the two signals are placed in quadrature.

By integrating the error signal into a measurement voltage with filtering circuitry having appropriate responsiveness to biological systems, a signal can therefore be sampled and compared frequently enough to dynamically monitor pulsatile components. Such circuitry simply requires the appropriate time constant and is commonly known in the field. The present invention also employs a relatively simple calibration method to convert the pulsatile components into ICP with a measurement baseline. The method involves tilting the head to a new position to cause a change in ICP of a known amount. The tilt also causes a change in the CSF pulsatile components, which causes a change in the error signal and associated measurement voltage. The change in known ICP divided by the associated change in measurement voltage allows a measurement baseline to be obtained and therefore

permits monitoring of the pulsatile components associated with subsequent changes in ICP. Since respiration pulses also affect intracranial pressure, a system which monitors blood gases can be used as an alternative calibration method should tilting the head be deemed undesirable.

Further, another possible calibration method to account for changes in the pulsatile components caused by changes in blood pressure could be achieved by correlating the change in measurement voltage with changes in blood pressure measured at a different point on the body, such as the wrist.

Brief Description of the Drawings

A more complete appreciation of the invention and the many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with accompanying drawings, wherein:

FIG. 1 is a simplified schematic diagram of the preferred measurement device;

FIG. 2A is a graphical representation of CSF pulsatile components in relation to measurement voltage;

FIG. 2B is another graphical representation of CSF pulsatile components in relation to measurement voltage; and

FIG. 3 is a simplified schematic diagram of a preferred measurement device.

Detailed Description of the Invention

The present invention employs a pulsed phase-locked-loop (PPLL) , which can be in the form of a constant frequency PPLL (CFPPLL) or a variable frequency PPLL (VFPPLL). FIG. 1 illustrates a simplified schematic diagram of essential components of the preferred embodiment for the non-invasive intracranial pressure monitoring system. As shown in FIG. 1 the present invention can preferably employ a CFPPLL measurement device 140 having a synthesizer 110 for generating an

electrical reference signal 150, and a transducer 130 for converting it into an acoustic reference signal 151. The transducer 130 transmits the acoustic reference signal 151 into the patient head 120 and it is reflected back to the transducer 130 in the form of a phase varied acoustic signal 152. The transducer 130 then converts the phase varied acoustic signal 152 into a phase varied electrical signal 153. Use of acoustics enables the method to be completely non-invasive. The phase variation in the acoustic signal 152 is a function of pulsatile variations in the CSF contained in the patient head 120. A phase detector 100 compares the phase of the electrical reference signal 150 and phase varied electrical signal 153. The output of the phase detector 100 is an error signal 200 which is proportional to the difference in phase from quadrature. The amount of voltage required to shift the phase of the electrical reference signal 150 to quadrature with the phase varied electrical signal 153 is obtained by the electrical integration of error signal 200 using integrator 116. Integrator 116 has a sufficient time constant to allow dynamic sampling and comparison of signals. A phase shifter 117 can be provided to perform the phase shift of the electrical reference signal 150 to quadrature with the phase varied electrical signal 153. Filtering circuitry 115 is responsive to biological systems and the result is a measurement voltage 201 that responds to the different timing requirements of the intracranial complex. That is to say, that in at least one embodiment the filtering circuitry 115 can be chosen to correspond to a particular biological system, e.g., pulse rate, respiration rate, etc.

FIG. 2A illustrates the relationship between the CSF pulsatile components 210 present in the patient head 120 and the measurement voltage 201 whose origin is taken from the phase detector 100. The measurement device 140 can be calibrated by tilting the patient head 120 such that a known change in ICP is induced. The tilt also induces a change in the CSF pulsatile components 210, which is sensed by the corresponding skull expansion, and an associated measurement voltage 201. By measuring the voltage 201, the CSF pulsatile components 210 can be inferred. By dividing the known change in ICP by the change in the measured control voltage 201,

a measurement baseline is obtained. The changes in the pulsatile components can therefore be dynamically converted into changes in ICP with the measurement baseline. FIG. 2B merely shows an inverted signal, as compared to FIG. 2A, which could result from an opposite polarity of the output voltage.

While the preferred embodiment employs a transducer 130 to transmit and receive the ultrasonic (acoustic) signals, any means for receiving an acoustic signal from the patient's head will suffice. Also, measurement devices other than a CFPPLL can be used as means for determining the pulsatile component of the acoustic signal, and associated ICP. In other possible embodiments of the present invention other known phase shifting capabilities of PPLLs can be utilized to monitor this variation in the CSF pulsatile components, for example, as explained in the article by Yost, et al. , *Fundamental Aspects of Pulse Phase-locked Loop Technology-based Methods for Measurement of Ultrasonic Velocity*, J. Acoust. Soc. Am. 91, 1456-1468 (1992), which article is incorporated herein by reference.

FIG. 3 illustrates a simplified schematic diagram of some of the essential components of a preferred embodiment for the non-invasive intracranial pressure monitoring system. FIG. 3 shows a PPLL measurement device 140A which can be in the form of a CFPPLL or a VFPPLL. As explained in more detail above, a transducer 130 can be placed on the side of a person's head as shown in FIG. 3. In at least one embodiment, this transducer can have a resonant frequency of less than about 1 megahertz, and generates an ultrasonic signal of about 500 kilohertz. The head can be tilted from one position to a new position. This tilting causes a change in ICP of a known amount. It also causes a change in error signal output 200 (for example, the sample and hold output 200 from the phase detector signal) which can go to the integrator and then to the phase shifter, as explained above. As a tilt causes a change in output voltage, it also causes a corresponding change in ICP. The change in ICP divided by the change in voltage permits the determination of the pulsatile components in the phase shifter output, thus the dynamic changes in ICP can be

determined. Filtering circuitry 115 can be responsive to biological systems and the result is a measurement voltage 201 that responds to the different timing requirements of the intracranial complex.

In constant frequency systems all of the functions can also be performed with digital electronics. As an example, rather than detecting the phase differences between the echo signal and reference signal, and using the integrated phase difference to drive the signals to quadrature, the echo signal and the reference signal can be digitally recorded, and the phase difference determined by use of computer algorithms. As further example, timing control, gating, waveform generation (synthesizer), coupling/decoupling function, and even the preamp function, can be performed by digital electronics or an appropriately programmed digital computer.

Various methods may be used to calibrate the present inventive device by providing known changes in ICP, as for example disclosed in U.S. Patent No. 5,617,873 issued to Yost et al. at column 5, line 32 thru column 6, line 14, which is incorporated herein by reference.

It should be understood by those skilled in the art that the descriptions and illustrations herein are by way of examples and the invention is not limited to the exact details shown and described. For example, it should be understood that any device that produces a controlled phase shift in response to a control signal may be used; for example, a current controlled phase shifter or an optically controlled phase shifter. Further, for example, any means of phase detection may be used, for example, a synchronous detector, a homodyne detector, an analog mixer, or a digital mixer.

What is claimed is:

1. A method for non-invasive measurement of changes in intracranial pressure in a patient's head comprising the steps of:

receiving an acoustic signal from the patient's head;

determining a pulsatile component of the acoustic signal; and

determining a change in intracranial pressure from changes in the pulsatile component.

2. The method for non-invasive measurement of changes in intracranial pressure of claim 1 wherein the step of determining a pulsatile component of the acoustic signal comprises:

determining a difference in phase between the acoustic signal and a reference signal;

generating a measurement voltage based on the difference in phase; and

monitoring the measurement voltage such that the pulsatile component of the acoustic signal can be determined.

3. The method for non-invasive measurement of changes in intracranial pressure of claim 2 wherein the step of determining intracranial pressure from the pulsatile component comprises:

calibrating a measurement device by inducing a known change in intracranial pressure and measuring the change in the measurement voltage;

dividing the known change in intracranial pressure by the change in the measurement voltage to obtain a measurement baseline; and

converting the change in pulsatile component into a change in intracranial pressure with the measurement baseline.

4. The method for non-invasive measurement of changes in intracranial pressure of claim 1 wherein the pulsatile component represents systolic blood pressure partially transferred to the cerebrospinal fluid.

5. The method for non-invasive measurement of changes in intracranial pressure of claim 1 wherein the pulsatile component represents diastolic blood pressure partially transferred to the cerebrospinal fluid.

6. An apparatus for non-invasive measurement of changes in intracranial pressure in a patient's head comprising:

means for receiving an acoustic signal from the patient's head;

means for determining a pulsatile component of the acoustic signal; and

means for determining changes in intracranial pressure from changes in the pulsatile component.

7. The apparatus for non-invasive measurement of changes in intracranial pressure in a patient of claim 6 wherein the means for determining a pulsatile component of the acoustic signal further comprises:

filtering circuitry with sufficient responsiveness to dynamically monitor the pulsatile component; and

a constant frequency pulse phase-locked loop measurement device.

8. The apparatus for non-invasive measurement of changes in intracranial pressure in a patient of claim 6 wherein the means for determining a pulsatile component of the acoustic signal further comprises:

filtering circuitry with sufficient responsiveness to dynamically monitor the pulsatile component; and

a variable frequency pulse phase-locked loop measurement device.

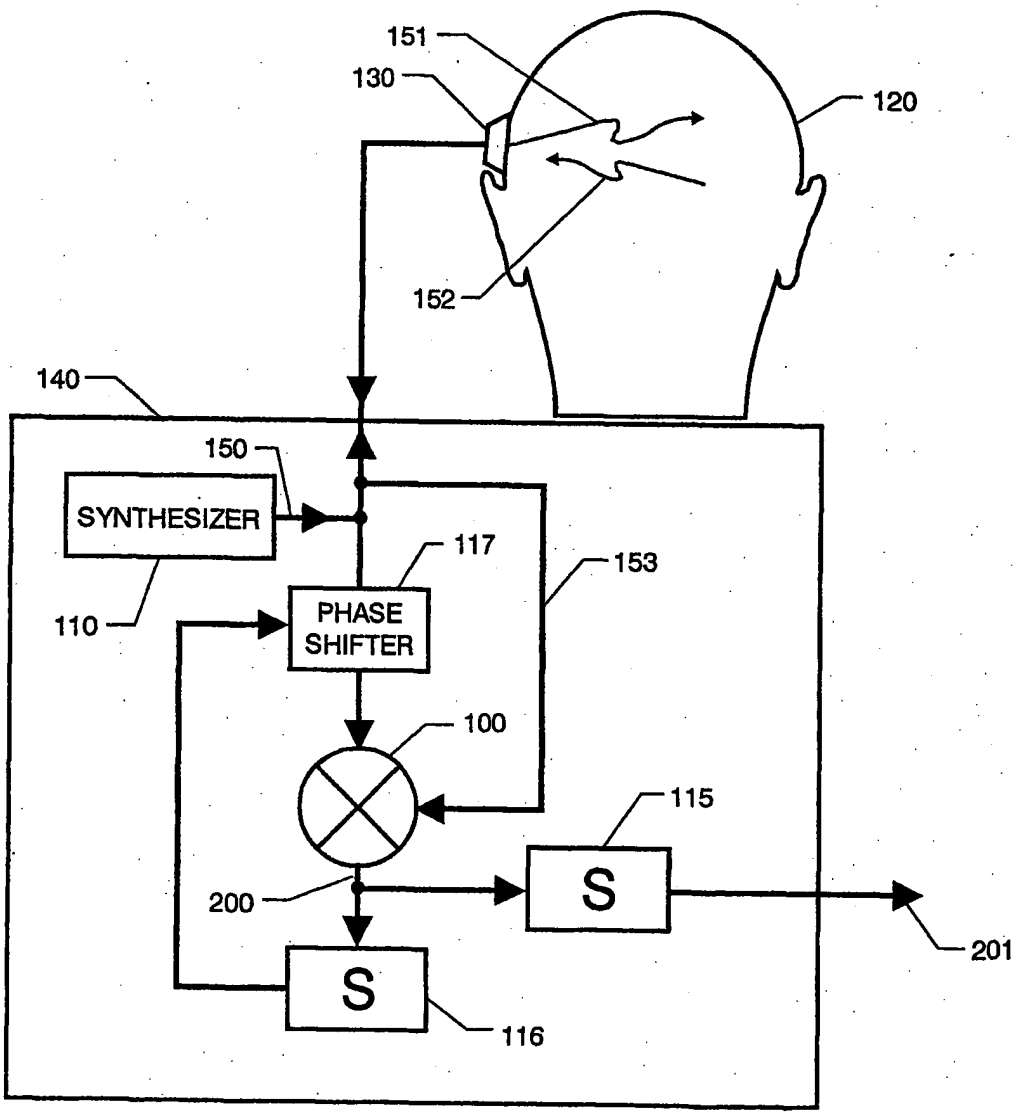

151
130
120
152
140
150
SYNTHESIZER
117
153
110
PHASE SHIFTER
100
115
S
200
201
S
116

FIG. 1

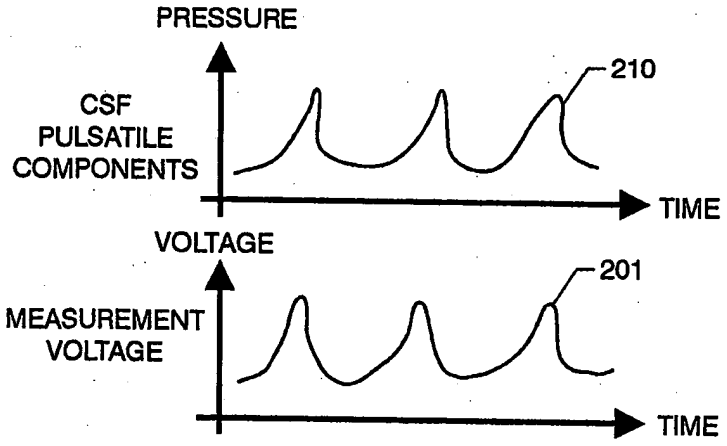

PRESSURE
CSF
PULSATILE
COMPONENTS
210
TIME
VOLTAGE
MEASUREMENT
VOLTAGE
201
TIME

FIG. 2A

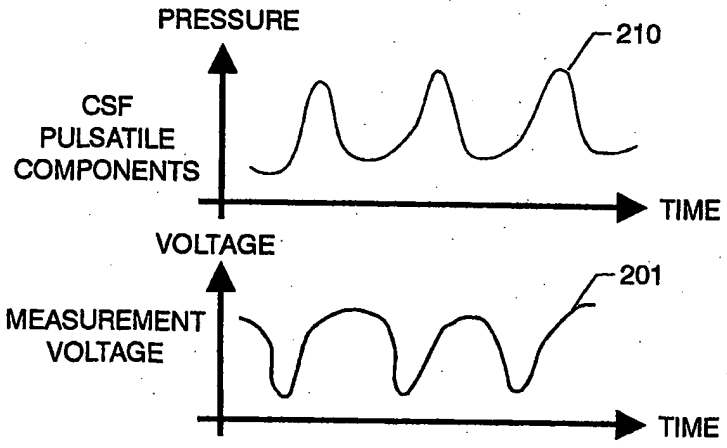

PRESSURE
CSF
PULSATILE
COMPONENTS
210
TIME
VOLTAGE
MEASUREMENT
VOLTAGE
201
TIME

FIG. 2B

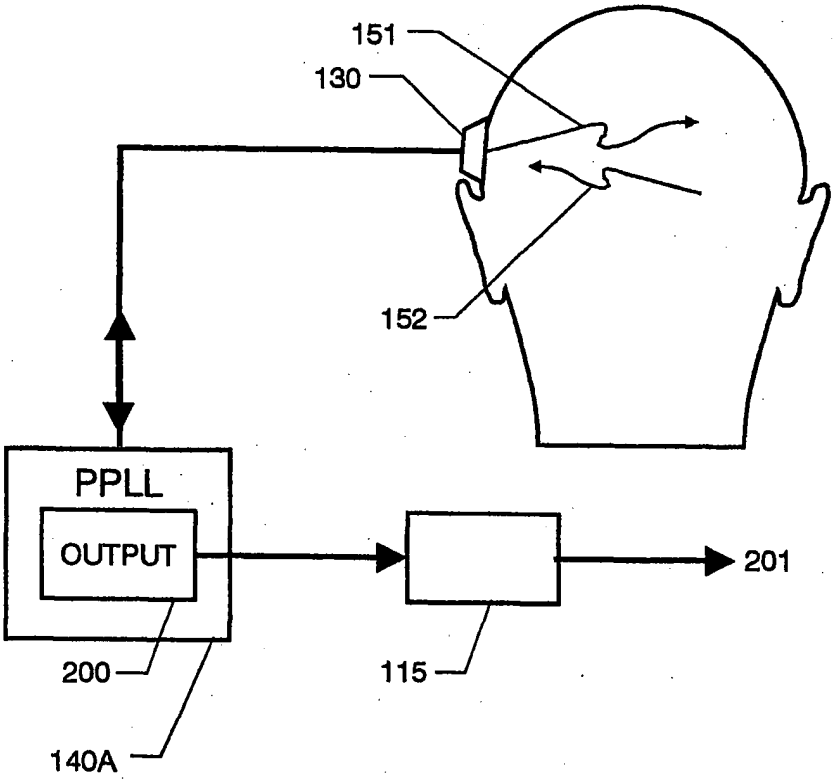


FIG. 3

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 00/02196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B8/08 A61B5/03

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 388 583 A (A. RAGAUSKAS ET AL) 14 February 1995 (1995-02-14) column 1, line 64 -column 3, line 59	1,6
Y	column 5, line 25 -column 6, line 12	2-5,7
Y	US 5 617 873 A (W. T. YOST ET AL) 8 April 1997 (1997-04-08) cited in the application column 5, line 8 - line 30	2,3,7
A	abstract	1,8
Y	US 4 703 758 A (YOSHIAKI OMURA) 3 November 1987 (1987-11-03) column 3, line 12 - line 27	4,5
A	US 4 971 061 A (NAOKI KAGEYAMA ET AL) 20 November 1990 (1990-11-20) column 2, line 26 -column 3, line 64	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2000	15/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Geffen, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Int al Application No
PCT/US 00/02196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5388583 A	14-02-1995	AT 182258 T	15-08-1999
		AU 7623294 A	22-03-1995
		DE 69419614 D	26-08-1999
		DE 69419614 T	02-03-2000
		EP 0717606 A	26-06-1996
		WO 9506435 A	09-03-1995
US 5617873 A	08-04-1997	NONE	
US 4703758 A	03-11-1987	EP 0276344 A	03-08-1988
US 4971061 A	20-11-1990	JP 1797443 C	28-10-1993
		JP 5003289 B	14-01-1993
		JP 63082622 A	13-04-1988
		DE 3750851 D	19-01-1995
		DE 3750851 T	13-07-1995
		EP 0413816 A	27-02-1991
		WO 8802233 A	07-04-1988